The biochemical control of the cell cycle by growth regulators in higher plants

TANG Wei, Latoya Harris, Ronald J. Newton

Department of Biology, Howell Science Complex, East Carolina University, Greenville, NC 27858-4353, USA

Abstract The cell cycle is an important research field in cell biology and it is genetically and developmentally regulated in animals and plants. The aim of this study was to review knowledge about the biochemical regulation of the cell cycle by plant growth regulators through molecular checkpoints that regulate the transition from G0-G1-S-phase and G2-M in higher plants. Recent research has shown that zeatin treatment led to the up-regulation of CycD3 in *Arabidopsis.* Benzyladenine treatment can also shorten the duration of S-phase through recruitment of latent origins of DNA replication. Kinetin is involved in the phosphoregulation of the G2-M checkpoint; the major cyclin-dependent kinase (Cdk) at this checkpoint has recently shown to be dephosphorylated as a result of cytokinin treatment, an effect that can also be mimicked by the fission yeast Cdc25 phosphatase. Gibberellic acid (GA) treatment induces internode elongation in deepwater rice, this response is mediated by a GA-induced up-regulation of a cyclin-Cdk at the G2-M checkpoint. Recent evidence has also linked abscisic acid to a cyclin-dependent kinase inhibitor. A new D-type cyclin, recently discovered in *Arabidopsis* may have a key role in this process. A brief review on plant growth regulator-cell cycle interfacing during development and a cytokinin-induced continuum of cell cycle activation through the up-regulation of a plant D-type cyclin at the G1 checkpoint and the phosphoregulation of the Cdk at the G2/M checkpoint had been concluded. This review could be valuable to research on cell and developmental biology in plants.

Key words: cell cycle, checkpoints, development, plant growth regulators

CLC number: Q942 **Document code:** A **Article ID:** 1007-662X(2004)03-0227-06

Introduction

Research on the cell cycle is very important in animals and plants because the cell cycle is a key biochemical process involved in growth, development, and differentiation of organisms. The cell cycle includes four distinctive phases: post-mitotic interphase (G1), DNA synthetic phase (S), post-synthetic interphase (G2) and mitosis (M-phase) (Francis et al. 2001). In addition, subdivisions of mitosis into M and cytokinesis and the existence of a non-cycling G1-phase (G0) are also important parts of cell cycle (Figure 1). The cell cycle represents a regulated running track stewarded by a series of checkpoints that determine whether or not the chromosomes are to be duplicated during S-phase and whether or not chromatids are ready to be partitioned during M-phase. The checkpoint was empirically defined by Hartwell and Weinert (Hartwell et al. 1989), that is, when step 'B' is dependent on the completion of step 'A', that dependence is governed by a checkpoint unless a loss-of-function mutation exists that relieves the dependence. For example, in budding yeast, the transition from G2 to M is dependent on intact DNA but the dependence is eliminated by deletion of the RAD9 gene making the latter a functional part of the checkpoint that monitors DNA integrity (Paulovich et al. 1997). If the checkpoint hurdle proves insurmountable, perhaps because the cell is too small or its DNA exhibits a catastrophic number of lesions, it arrests more or less permanently, or it enters programmed cell death (Levine 1997) or it rests temporarily making necessary repairs before rejoining the race. However, in different situations, cell division can drive expansion, or expansion can drive division (Jacobs 1997). Whatever the developmental outcome, proliferative cells in a meristem must pass a number of checkpoints in order to be competent to divide. The regulation of the cell cycle is a very complicated process. This overview mainly describe: 1) the cell cycle and checkpoints; 2) cytokinins and the cell cycle; 3) auxin and the cell cycle; 4) gibberellins and the cell cycle. The aim is to provide an overview on the growing literature about the effects of plant growth regulators on molecular checkpoints in the plant cell cycle. This review could be valuable to understand more about the checkpoints of the cell cycle and how they respond to extracellular growth factors.

The cell cycle and checkpoints

There are a number of checkpoints in the animal and yeast cell cycle and there may be a similar number in the plant cell cycle. Each checkpoint comprises a cyclin dependent protein kinase (Cdk) that can only exhibit catalytic activity when bound to a partner protein, a cyclin (Figure 2).

Biography: TANG Wei (1964-), male, Ph. Doctor, V. Assistant Professor, Department of Biology, Howell Science Complex, East Carolina University, Greenville, NC 27858-4353, USA. Tel: (252)-328-2021; Fax: (252)-328-4178; E-mail: tangw@mail.ecu.edu
Received date: 2002-01-06
Responsible editor: Chai Ruihai

The G1/S-phase transition is best understood in budding yeasts and vertebrate cells and the G2/M transition in fission yeast (Figure 1). The former checkpoint comprises Cdk4/6-cyclinD and Cdk2-cyclinE while the latter consists of Cdk1 kinase cyclinB and Cdk1-cyclinA (Sherr 1993; Norbury *et al.* 1992). The scene set by animal and yeast cell cycle data clearly depicts each checkpoint as a multi-component fail-safe and a remarkably fastidious monitor of the cell's competence for division (Figure 2). In addition, elaborate feedback controls form a complex mechanism sensing the integrity of DNA and ensuring a tight coupling between DNA replication and cell division (Paulovich *et al.* 1997). The decision to proliferate or not is the most critical decision in the life of a cell; therefore, the complexity of cell cycle checkpoints was describe elegantly by Berridge (Berridge 1995). In animals and yeasts, cell cycle checkpoints are sensitive to nutrient status and growth factors, which can induce calcium signals that impinge on the cell cycle (Elledge 1996). It seems that extracellular signaling mechanisms operate at the level of G0-G1-S-phase in animal cells and yeasts, whereas recent work in plants suggests that plant growth regulators affect both G0-G1-S-phase and the G2-M transition. This becomes increasingly important to discover the molecular nature of checkpoints in the plant cell cycle. Hence, the aims of this review are to consider major transition points of the plant cell cycle: G0-to-G1, G1-to-S-phase and G2-to-M, and to try and integrate what is known about the effects of plant growth regulators at these transitions with the function of particular checkpoints.

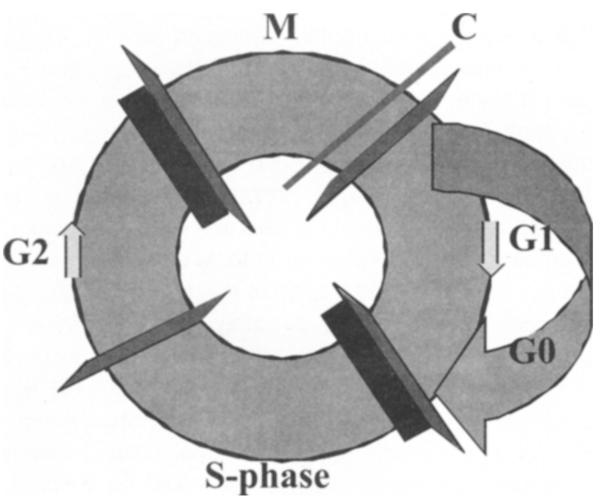

Fig. 1 Schematic of the eukaryotic cell cycle including mitosis (M-phase), cytokinesis (C), post-mitotic interphase (G1), and the side-branch for non cycling cells to arrest in G0, S-phase (period of DNA synthesis) and G2 (post synthetic interphase). The shaded boxes, adhering to the Principal Control Point Hypothesis, mark the positions of the key checkpoints of the cell cycle, G1-to-S, and G2-to-M.

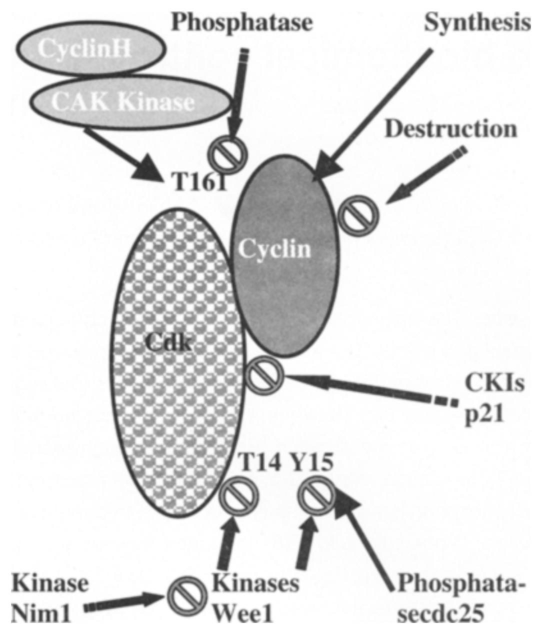

Fig. 2 Schematic of a generalised checkpoint of the eukaryotic cell cycle featuring a cyclin-dependent protein kinase (Cdk) bound to a cyclin protein.
Phosphorylation of threonine161 of the Cdk by a cyclin-dependent activating kinase (CAK kinase) leads to binding of the Cdk with the cyclin, this binding can be repressed by phosphatase activity. Most cyclin proteins rise in concentration through the cell cycle, such as cyclinB peaks in late G2 and M-phase before rapid ubiquitin-dependent proteolysis that in turn incapacitates the Cdk's catalytic activity. The Cdk is phosphoregulated on threonine14 and tyrosine15 residues; *cdc25* and *wee1* are given as fission yeast examples of the phosphatases and kinases that are involved. In turn in fission yeast, Wee1 kinase can be repressed by a protein kinase encoded by Nim1 kinase. The activity of the cyclin-dependent kinase is also repressed by cyclin-dependent protein kinase inhibitors (CKIs) [adapted from Elledge (1996)].

Cytokinins and the cell cycle

Cytokinins were first discovered in herring sperm DNA extract (Miller *et al.* 1955). This class of plant growth regulators promotes plant cell division when they are added exogenously to plant organs or when added to tissue culture media. Such as kinetin and benzyladenine, can stimulate cell division and shorten cell cycles if added exogenously to cultured cells. Cytokinin treatment can cause non-cycling cells to divide and can act at the G1/S-phase transition. For example, benzyladenine (20 μM), and indole butyric acid (0.1 μM) stimulated formerly quiescent G0 cells into S-phase in dormant buds of *Fraxinus* (Nougarede *et al.* 1996). Cytokinins may also increase the proportion of rapidly cycling cells in meristems by inducing G0 cells to enter the cell cycle (Gonthier *et al.* 1987). Although in plants, cells can arrest in G2, most data show

G0 (non-cycling G1) as the resting-place for the majority of non-cycling cells both in plants and animals. As mentioned above, cytokinin treatment can cause cells to undergo the G0-to-G1 transition. Plant D-type (CycD) cyclins were first isolated from *Arabidopsis* and alfalfa by their ability to functionally complement yeast strains defective in G1 cyclin activity (Dahl *et al.* 1995; Soni *et al.* 1995). Subsequently, over 20 CycD genes have been isolated from a range of species (Murray *et al.* 1998; Renaudin *et al.* 1996; Sorrell 1999). Based on sequence criteria, these cyclins are classified into three distinct groups, CycD1, CycD2 and CycD3, originally defined in *Arabidopsis* (Renaudin *et al.* 1996; Sorrell 1999). Recently, a new *Arabidopsis* CycD (CycD4) has been isolated, which, based on a limited sequence analysis was classified as being the first member of a new CycD4 group (De Veylder *et al.* 1999). Similar to animal D-type cyclins, plant CycDs contain the characteristic LxCxE Rb-binding motif. The majority of CycDs show expression patterns reminiscent of animal D-type cyclins, including rapid transcript accumulation when quiescent cells in suspension culture are stimulated with growth promoting substances, suggesting that they also regulate G1 progression in response to extracellular signals (Doonan 1998; Riou-Khamlichi *et al.* 1999; Sorrell *et al.* 1999a). A landmark study on *Arabidopsis* CycD3 demonstrated that CycD3 transcripts were found to be elevated in *Arabidopsis* mutants with high cytokinin levels and could be rapidly induced by the exogenous application of cytokinin in cell cultures (optimally with 1–10 μM zeatin or 1 μM benzylaminopurine) and in intact plants (1 μM zeatin). Moreover, in cultured leaf explants taken from transgenic plants constitutively expressing CycD3, cell division could be induced and maintained, in the absence of exogenous cytokinin. Current data obtained using cell cultures suggest that sucrose may stimulate G0-to-G1 progression by rapidly inducing CycD2 (Sorrell *et al.* 1999b). Plant CycD cyclins have been shown to interact with plant Rb proteins, via the LxCxE motif (Ach *et al.* 1997; Huntley *et al.* 1998), which, in turn, interact with recently identified plant E2F homologues (Ramirez-Parra *et al.* 1999; Sekine *et al.* 1999). Therefore, it seems highly likely that CycD cyclins, like animal D-type cyclins, regulate G1 progression via an Rb-E2F based mechanism. However, the exact details of this mechanism involved in providing a cytokinin-induced continuum from G0 through to S-phase remain to be determined.

During the DNA replication, there is the activation of multitudes of replication origins spaced along the DNA molecule. From each origin, two replication forks diverge until they meet with forks from adjacent origins. The origin and its two diverging forks are known as a replicon (Taylor 1963; VantHof 1987). Clear evidence also exists for activation of latent origins of DNA replication by exogenous application of cytokinins. A single application of benzyl adenine (4.5 μM) to vegetative shoot apices of *Sinapis alba* resulted in a 50% shortening in replicon size from 15 to 7.5 μM (Houssa *et al.* 1990). One other intriguing effect of applying cytokinins to shoot apices of *Sinapis alba* was the 100% synchronous activation of replication origins. Hence, cytokinins must participate in or trigger signal transduction chains that result in activation of latent replication origins. In budding yeast, this cascade of proteins acts downstream of CDC28-G1 cyclins (Jiang *et al* 1997; Jackson *et al* 1993). As elegantly shown by Jacqmard and her colleagues (Jacqmard *et al.* 1995) plant growth regulators also activate, inactivate, and initiation points for DNA replication through alterations of the DNA loops at the nuclear matrix.

In fission yeast, DNA-dependent protein kinases (Rhind *et al.* 1993) have been identified as important players in the repair process at the G1-to-S and G2-to-M checkpoints. In plants, VantHof (1973) showed that the G2-to-M, and G1-to-S transitions could be blocked by denying cells an energy source through removal of carbohydrate from the medium, by exposing cells to inhibitors of protein synthesis, Fosket et al. (Fosket 1997) observed that in soybean, zeatin (0.5 μM) caused qualitative changes in protein synthesis and concluded that these changes were necessary to permit the entry of cells into division. More recently, in tobacco TBY-2 cells, peaks of zeatin, zeatin riboside and zeatin-50 monophosphate levels were observed to coincide with the end of S-phase, mitosis and G1-phase (Laureys *et al.* 1998; Redig *et al.* 1996). The involvement of cytokinins at the G2-to-M phase transition was also shown in *Nicotiana plumbaginofolia* cells in culture (Zhang *et al.* 1996). Cells that arrested in G2, because of a lack of cytokinin, exhibited high levels of inactive Cdc2 which was phosphorylated at tyr15 (Zhang *et al.* 1996). One immediate consequence of cytokinin (0.23 μM kinetin) induced entry into M-phase was dephosphorylation of Cdc2. Subsequently, the same workers observed that this dephosphorylation could also be mediated by fission yeast Cdc25 phosphatase (Zhang *et al.* 1996). Each protein that influences Cdk activity is a potential interface for signal transduction pathways. This thereby represents the core of a cytokinin-dependent activation of cells into mitosis. The transition from G2-to-M in the plant cell cycle is made more complicated because, in addition to stopping in G0, plant cells can arrest in G2. For example, meristematic cell arrest in G2 occurs in *Vicia faba* (VantHof *et al.* 1973), *P. sativum* (Evans *et al.* 1973, 1974; Mazzuca *et al.* 1997) and *Lactuca sativa* (Mazzuca *et al.* 1997). Cell arrest in G2 was pronounced in response to trigonelline, a substance that is synthesized in the cotyledons and transported to the root system (Evans *et al.* 1973, 1974).

Auxin and the cell cycle

The shoot apical meristem is a dome of cells that perpetually changes its shape. It gets bigger through cell division during a plastochron and drops back to a smaller size upon initiation of primordia (Lyndon 1977). During the transition to floral growth the apex enlarges maximally and is due to a substantial increase in the rate of cell division

(Francis *et al.* 1985). An involvement of plant growth regulators in regulating shoot apical cells could be through altering the kinetics of cell division through checkpoints. Green (Green 1994) identified the organization of cell wall microfibrils as key elements in the control of organ initiation. As pointed out previously (Francis 1998), such changes in surface microstructure ought to be coupled with changes in the plane of cell division for a cohort of peripheral zone cells that is destined to form the new primordium. IAA can change the mechanical properties of cell walls (Masuda 1990) and alter the orientation of cortical microtubules (Shibaoka 1994). Auxins and the cell cycle in terms of regulating planes of cell division interface at the level of microtubule associated proteins and mitogen associated protein kinases (Vantard *et al.* 1998). Using radish roots, Blakely *et al.* (1982) demonstrated that lateral forming had been regulated by exogenous IAA. Polar transport of auxin from shoot to root is also a well-established phenomenon and, hence, triggering of cell division by auxin in the pericycle, became an attractive hypothesis (Scott 1972). The movement of this plant growth regulator is probably bi-directional in the root system moving up in one tissue while moving down in another (Mitchell *et al.* 1975; Tsurumi *et al.* 1978). These elegant studies from the 1970's proved very useful for the genetic analyses of the 1990's that have employed *auxin* deficient mutants and auxin over-producing mutants of *Arabidopsis* (Berridge 1995).

Mutants with abnormal levels of IAA make an excess number of lateral roots and adventitious roots (*alf1*) (Celenza *et al.* 1995). Another is defective in lateral root formation (*alf4-1*). Applications of IAA to ALF4 plants led to lateral root formation. Studies of other mutant phenotypes, which can initiate primordia that develop no further, led to the conclusion that the development of the primordium across the cortex is a separately controlled event (Celenza *et al.* 1995). When the promoter of *cdc2aAt* was used to drive GUS expression, *Arabidopsis* roots exhibited not only an intensely stained primary root meristem but also a prominently stained pericycle along its entire length (Hemerly *et al.* 1993), which is consistent in showing the mitotic competence of this tissue.

Gibberellins and the cell cycle

GA-induced growth depends on an increase in both the rate of cell elongation and the rate of cell production in the intercalary meristem (Bleeker *et al.* 1986; Sauter *et al.* 1992). The initial response was an increase in cell size followed by an activation of G2 cells into mitosis and then an increase in the rate of DNA synthesis. The data were clear consistent with an induction of cell cycle activation at the G2/M transition and subsequent entry of these cells into S-phase (Sauter *et al.* 1992). Two rice cyclin homologues were also up-regulated that led to the conclusion that GA treatment resulted in transcriptional activation of G2-M checkpoint proteins (Sauter *et al.* 1995). Indeed, the cell cycle was longer in meristems treated with exogenous GA3 (290 μM) compared with the untreated controls (Daykin *et al.* 1997). The major effect of applied GA3 on cell division was in the developing internode. In the GA3 treatment (290 μM), cell doubling times in the epidermis, cortex and pith were about half that of the controls. It seems that internodal growth in both a monocot and dicot is regulated, at least in part, by a GA induced increase on the rate of cell production and that this plant growth regulators impinges on the G2-M checkpoint at the level of the Cdc2 kinase (Sauter *et al.* 1995).

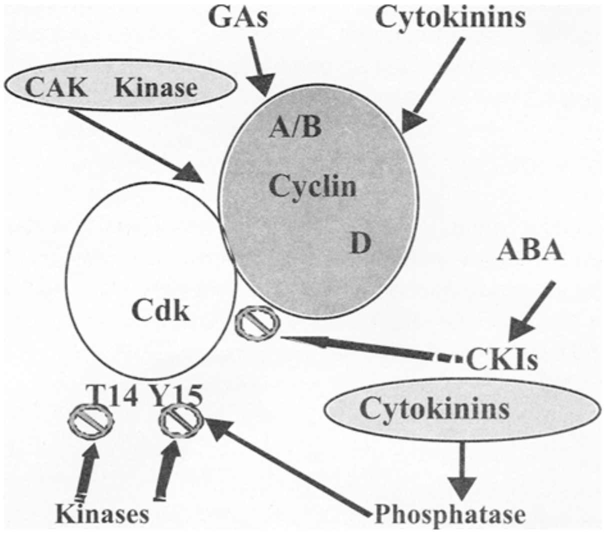

Fig. 3 Schematic of a plant cell cycle checkpoint with known interfaces between the checkpoint and plant growth regulators (Francis *et al.* 2001). The schematic indicates up-regulation of cyclin A/B by gibberellins (Sauter *et al.* 1995), of D-type cyclins by cytokinins (Soni *et al.* 1995) of cyclin dependent kinase inhibitors (CKIs) by abscisic acid (Wang *et al.* 1997), and of cytokinin-activated phosphatases that dephosphorylate tyrosine15 of the Cdk (Zhang *et al.* 1996).

Conclusions

Understanding plant growth regulator-cell cycle interfacing will provide a unique insight into both cell cycle control and the development of plants. Moreover, such an understanding will help us appreciate the evolutionary divergence of cell cycle checkpoints in plants, yeasts and animals. There are interfaces between cell cycle checkpoints and cytokinins, gibberellic acid, and abscisic acid (Figure 3). The discovery of plant homologues to regulatory genes of the cell cycle will widen the possibility of testing the level at which plant growth regulators are involved with the checkpoints (Francis *et al.* 2001). Establishing a wider base of plant homologues to MCMs, Cdc6p and Cdc7p is now necessary in order to test the molecular circuitry and at which level DNA replication is most sensitive to plant

growth regulator-mediated signal transduction chains. There is an exciting story of interfacing between plant growth regulators and the cell cycle. Francis and Sorrell (2001) had invoked models to engage a specific plant growth regulator with a particular cell cycle checkpoint (Figure 3), but the interaction of each plant growth regulator with its receptor and the events down-stream of receptor binding that impinge on the cell cycle remain to study. Discovering plant homologues to vertebrate and yeast cell cycle genes is important, but determining their function will require a clear understanding of cell cycle interfaces. Indeed Trewavas (1985) pointed out that whilst growth substances are part of the genetic potential for rapid cell division, that potential can only be fulfilled if other resources such as nutrient, calcium signalling are supplied adequately.

References

Ach, R.A., Durfee, T., Miller, A.B., Zambryski, P.C. and Gruissem, W. 1997. *RRB1* and *RRB2* encode maize retinoblastoma-related proteins that interact with a plant D-type cyclin and geminivirus replication protein [J]. Mol. Cell Biol., **17**: 5077–5086.

Berridge, M.J. 1995. Calcium signalling and cell proliferation [J]. Bioessays **17**: 491–500.

Blakely, .L.M., Durham, M., Evans, T.A. and Blakely, R.M. 1982. Experimental studies on lateral root formation in radish seedlings. I General methods, developmental stages, and spontaneous formation of laterals [J]. Bot. Gaz., **143**: 341–352.

Bleeker, A.B., Schuette, J.L. and Kende, H. 1986. Anatomical analysis of growth and developmental patterns of deepwater rice [J]. Planta, **169**: 490–497.

Celenza, J.L., Grisafi, P.L. and Fink, G.R. 1995. A pathway for lateral root formation in *Arabidopsis thaliana* [J]. Genes Dev., **9**: 2131–2142.

Dahl, M., Meskiene, I., Bögre, L., Ha, D.T.C., Swoboda, I., Hubmann, R., Hirt, H. and Heberle-Bors, E. 1995. The D-type alfalfa cyclin gene *cycMs4* complements G1 cyclin-deficient yeast and is induced in the G1 phase of the cell cycle [J]. Plant Cell, **7**: 1847–1857.

Daykin, A., Scott, IM., Causton, D.R. and Francis, D. 1997. Gibberellin does not accelerate rates of cell division in the dwarf pea shoot apical meristem [J]. J. Exp. Bot., **48**: 1147–1150.

De Veylder, L., Almedia Engler, J de, Burssens, S, Manevski, A, Lescure, B, Van Montague, M, Engler, G and Inze, D 1999. A new D-type cyclin of *Arabidopsis thaliana* expressed during lateral root primordia formation [J]. Planta, **208**: 453–462.

Doonan, J.H. 1998. Cell division during floral morphogenesis in *Antirrhinum majus* [C]. In: Francis D, Dudits D and Inzé D. (eds) Plant Cell Division. London: Portland Press, pp 207– 222.

Elledge, S.J. 1996. Cell cycle checkpoints: preventing an identity crisis [J]. Science, **274**: 1664–1672.

Evans, L.S. and VantHof, J. 1973. Cell arrest in G2 in root meristems [J]. Exp. Cell Res., **82**: 471–473.

Evans, L.S. and VantHof, J. 1974. Promotion of cell arrest in root and shoot meristems in *Pisum* by factor from the cotyledons [J]. Exp. Cell Res. **87**: 259–264.

Fosket, D.E. 1977. Regulation of the cell cycle by cytokinin [C]. In: Rost TL (eds) Mechanism and Control of Cell Division. Stroudsberg Pennsylvania: Dowden, Hutchinson and Ross, pp 62–91.

Francis, D. 1998. Cell size and organ development in higher plants [C]. In: Francis D, Dudits D and Inze D (eds) Plant Cell Division. Colchester: Portland Press, pp 187–206.

Francis, D. and Lyndon, R.F. 1985. The control of the cell cycle in relation to floral induction. In: Bryant JA (eds) The Cell Division Cycle in Plants. Cambridge: Cambridge University Press, pp 199–215.

Francis, D. and Sorrell, D. 2001. The interface between the cell cycle and plant growth regulators: a mini review [J]. Plant Growth Reg., **33**: 1–12.

Gonthier, R., Jacqmard, A. and Bernier, G. 1987. Changes in cell cycle duration and growth fraction in the shoot meristems of *Sinapis* during floral transition [J]. Planta, **170**: 55–59.

Green, P.B. 1994. Connecting gene and hormone action to form, pattern and organogenesis: biophysical transduction [J]. J. Exp. Bot. **45** (special issue): 1775–1788.

Hartwell, L.H. and Weinert, T.A. 1989. Checkpoints: controls that ensure the order of cell cycle events [J]. Science, **246**: 629– 634.

Hemerly, A.S., Ferreira, P., Van Montague, M., Engler, G. and Inze, D. 1993. cdc2a expression in *Arabidopsis* is linked with competence for cell division [J]. Plant Cell, **5**: 1711–1723.

Houssa, C., Jacqmard, A. and Bernier, G. 1990. Activation of replicon origins as possible targets for cytokinins in shoot meristems of *Sinapis* [J]. Planta, **181**: 324–326.

Huntley, R., Healy, S., Freeman, D., Lavende,r P., de Jager, S., Greenwood, J., Makkerh, J., Walker, E., Jackman, M., Xie, Q., Bannister, A.J., Kouzarides, T., Gutiérrez, C., Doonan, J.H. and Murray, J.A.H. 1998. The maize retinoblastoma protein homologue ZmRb-1 is regulated during leaf development and displays conserved interactions with G1/S regulators and plant cyclin D (CycD) proteins [J]. Plant Mol. Biol., **37**: 155–169.

Jackson, A.L., Pahl, P.M., Harrison, K., Rosamond, J. and Sclafani, R.A. 1993. Cell cycle regulation of the yeast Cdc7 protein kinase by association with the Dbf4 protein [J]. Mol. Cell Bio., **13**: 2899–2908.

Jacobs, T.W. 1997. Why do plant cells divide? [J]. Plant Cell, **9**: 1021–1029.

Jacqmard, A., Houssa, C. and Bernier, G. 1995. Abscisic acid antagonizes the effect of cytokinin on DNA-replication origins [J]. J. Exp. Bot., **46**: 663–666.

Jiang, W. and Hunter, T. 1997. Identification and characterization of a human protein kinase related to budding yeast Cdc7p [J]. Proc Natl Acad Sci USA, **94**: 14320–14325.

Laureys, F., Dewitte, W., Witters, E., Van Montague, M., Inze, D. and Van Onckelen, H. 1998. Zeatin is indispensable for the G2-M transition in tobacco BY-2 cells [J]. FEBS Lett., **426**: 29– 32.

Levine, A.J. 1997. p53, the cellular gatekeeper for growth and division [J]. Cell, **88**: 323–331.

Lyndon, R.F. 1977. Interacting processes in development at the shoot apex [J]. Symp SEB., **31**: 221–250.

Masuda, Y. 1990. Auxin-induced cell elongation and cell wall changes [J]. Bot. Mag., **103**: 345–370.

Mazzuca, S., Bitonti, M.B., Pranno, S. and Innocenti, A.M. 1997. Nuclear metabolic changes in root meristem of *Lactuca sativa* induced by trigonelline [J]. Cytobios, **89**: 39–50.

Miller, C.O., Skoog, F., and Strong, F.M. 1955. Kinetin, a cell division factor from deoxyribonucleic acid [J]. J. Am. Chem. Soc., **77**: 1392.

Mitchell, E.K. and Davies, P.J. 1975. Evidence for three different systems of movement of indoleacetic acid in intact roots of *Phaseolus coccineus* [J]. Physiol. Plant, **33**: 290–294.

Murray, J.A.H., Freeman, D., Greenwood, J., Huntley, R., Makkerh, J., Riou-Khamlichi, C., Sorrell, D.A., Cockcroft, C., Carmichael, J.P., Soni, R. and Shah, Z.H. 1998. Plant D cyclins and retinoblastoma

protein homologues [C]. In: Francis D, Dudits D and Inzé D (eds) Plant Cell Division. London: Portland Press, pp 99–127.

Norbury, C. and Nurse, P. 1992. Animal cell cycles and their control [J]. Ann. Rev. Biochem., **61**: 441–470.

Nougarede, A., Silveira, C.E. and Rondet, P. 1996. In nature dormant buds and *in vitro* dormant-like buds of *Fraxinus excelsior* L [J]. Protoplasma, **190**: 16–24.

Paulovich, A.G., Toczyski, D.P. and Hartwell, L.H. 1997. When checkpoints fail [J]. Cell, **88**: 315–321.

Ramírez-Parra, E., Xie, Q., Boniotti, M.B. and Gutierrez, C. 1999. The cloning of plant E2F, a retinoblastoma-binding protein, reveals unique and conserved features with animal G1/S regulators [J]. Nucleic Acids Res., **27**: 3527–3533.

Redig, P., Shaul, O., Inze, D., Van Montague, M. and Van Onckelen, H. 1996. Levels of endogenous cytokinins, indole- 3-acetic acid and abscisic acid during the cell cycle of synchronised tobacco BY-2 cells [J]. FEBS Lett., **391**: 175–180.

Renaudin, J.-P., Doonan, J.H., Freeman, D., Hashimoto, J., Hirt, H., Inzé, D., Jacobs, T., Kouchi, H., Rouzé, P., Sauter, M., Savouré, A., Sorrell, D.A., Sundaresan, V. and Murray, J.A.H. 1996. Plant cyclins: unified nomenclature for plant A-, B- and D-type cyclins based on sequence organization [J]. Plant Mol. Biol., **32**: 1003–1018.

Rhind, P. and Russell, P. 1998. Mitotic DNA damage and replication checkpoints in yeast [J]. Curr Op Cell Biol., **10**: 749–758.

Riou-Khamlichi, C., Huntley, R., Jacqmard, A. and Murray, J.A.H. 1999. Cytokinin activation of *Arabidopsis* cell division through a D-type cyclin [J]. Science, **283**: 1541–1544.

Sauter, M. and Kende, H. 1992. Gibberellin-induced growth and regulation of the cell division cycle in deepwater rice. Planta 188: 362–368.

Sauter, M., Mekhedov, S.L. and Kende, H. 1995. Gibberellin promotes histone H1 kinase activity and the expression of cdc2 and cyclin genes during the induction of rapid growth in deepwater rice internodes [J]. Plant Journal, **7**: 623–632.

Scott, T.K. 1972. Auxins and roots. Ann Rev Plant Physiol 23: 235–258.

Sekine, M., Ito, M., Uemukai, K., Maeda, Y., Nakagami, H. and Shinmyo, A. 1999. Isolation and characterisation of the E2Flike gene in plants [J]. FEBS Lett., **460**: 117–122.

Sherr, C.J. 1993. Mammalian G1 cyclins [J]. Cell, **73**: 1059–1065.

Shibaoka, H. 1994. Plant hormone-induced changes in the orientation of cortical microtubules: Alterations in the crosslinking between microtubules and the plasma membrane [J]. Ann. Rev. Plant. Physiol. Plant Mol. Biol., **45**: 527–544.

Soni, R., Carmichael, J.P., Shah, Z.H. and Murray, J.A.H. 1995. A family of cyclin D homologs from plants differentially controlled by growth regulators and containing the conserved retinoblastoma protein interaction motif [J]. Plant Cell, **7**: 85– 103.

Sorrell, D.A. 1999. CycD cyclins and cyclin-dependent kinases in tobacco BY-2 cells [D]. PhD thesis, Cambridge University, UK.

Sorrell, D.A., Combettes, B., Chaubet-Gigot, N., Gigot, C. and Murray, J.A.H. 1999a. Distinct cyclin D genes show mitotic accumulation or constant levels of transcripts in tobacco Bright Yellow-2 cells [J]. Plant Physiol., **119**: 343–351.

Sorrell, D.A., Riou-Khamlichi, C., Chaubet-Gigot, N., Combettes, B., Gigot, C. and Murray, J.A.H. 1999b. Plant D-type (CycD) cyclins and the regulation of the plant cell cycle [C]. In: Altmann, A, (eds) Plant Biotechnology and in vitro Biology in the 21th Century. Dordrecht: Kluwer Academic Publishers, pp 441–444.

Taylor, J.H. 1963. DNA synthesis in relation to chromosome reproduction and the reunion of breaks [J]. J Cell Comp Physiol., **62**: 73–80.

Trewavas, A.J. 1985. Growth substances, calcium and the regulation of the cell cycle [C]. In: Bryant JA (eds) The Cell Division Cycle in Plants. Cambridge: Cambridge Univ Press, pp 133–156.

Tsurumi, S. and Ohwaki, Y. 1978. Transport of 14C-labeled indoleacetic acid in Vicia root segment [J]. Plant Cell Physiol., **19**: 1195–1206.

Vantard, M., and Lambert, A.-M. 1998. Cell cycle dependent nucleation and assembly of plant microtubular proteins [C]. In: Francis D, (eds) Plant Cell Division. Colchester UK: Portland Press, pp 301–318.

VantHof, J. 1973. The regulation of cell division in higher plants [J]. Brookhaven Symp, **25**: 152-165.

VantHof, J. 1987. Functional chromosomal structure: the replicon [C]. In: Bryant J and Dunham VL (eds) DNA replication in Plants. Boca Raton, Florida: CRC Press, pp 1–16.

VantHof, J., Hoppin, D.P. and Yagi, S. 1973. Cell arrest in G1 and G2 of the mitotic cell cycle of *Vicia faba* root meristems [J]. Am. J. Bot., **60**: 889–895.

Wang, H., Fowke, L.C. and Crosby, W.L. 1997. A plant cyclindependent kinase inhibitor gene [J]. Nature, **386**: 451.

Zhang, K., Letham, D.S. and John, P.C.L. 1996. Cytokinin controls the cell cycle at mitosis by stimulating the tyrosine dephosphorylation and activation of p34cdc2-like H1 histone kinase [J]. Planta, **200**: 2–12.